NON-INVASIVE PRENATAL TESTING (NIPT) FOR “OTHER” DISORDERS - ETHICAL CONSIDERATIONS

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Considerable experience of using NIPT in mainstream clinical practice.

Test performance in clinical settings is consistent.

Main use is in screening for T13,18 and 21

Some use of fetal sex determination for X-linked disorders.

Isolated cases at present of screening for single gene disorders such as achondroplasia in women at high risk.
Implementation statements

- **ACOG 2012**
  - Not to be offered to low risk women.
  - Indications – AMA, ultrasound features, previous affected child (high risk women).

- **SOGC 2013**
  - Offer to high risk women as an alternative to amniocentesis
  - BUT amniocentesis to confirm positive results before TOP

- **International Society of Prenatal diagnosis**
  - Offer to high risk women as a second line screen
  - Local economic resources and access to ultrasound, invasive testing and counselling should be taken into account.
In Canada and parts of UK NIPT is 2nd level contingent screening test for women at risk for T13, 18 and 21
NIPT - Advantages

- Better accuracy than current prenatal screening tests (99% for T21, 97% for T18, 90% for T13 with 0.3% false +ve rate).
- More available – blood test
- Less discomfort than amnio/CVS
- No miscarriage risk
NIPT- Disadvantages

- Cost
- Test failures
- Unclear result due to mosaicism
- Confirm positive result with amnio, i.e. not diagnostic test
- ? Multiple pregnancy
- Does not provide information on cardiac defects (NT) and PET risk (T2 biochemistry).
Test failures

- Low fetal fraction
  - Average number of cfDNA in maternal blood is 10%
  - Need at least 4% for reliable result
  - Lower fraction in *obese patients* and *Afro-Caribbean*.
  - Relevant in SA context

- Unsuitable samples

- Failed quality control. Usually get result on re-testing.
A risk free blood test for Down syndrome in pregnancy

A breakthrough which could lead to Down syndrome becoming extinct.

Controversial prenatal Down syndrome test gets go ahead in Switzerland raising fears of spike in abortions.

Blood test for mothers could save lives of hundreds of unborn babies.
85% of reporting was about T21, but some reporting included single gene disorders.

Test benefits were highlighted.

Not balanced with concerns. Only 1/3 were balanced.

Focus on NIPT becoming routine for all women.

Doctors saw test positively; patient groups had mixed views.
Some inaccuracies

- Describing it as a diagnostic test
- Pinprick test
- Not addressed that invasive testing gives more comprehensive result than NIPT
- Used to diagnose haemophilia (only used to determine sex)
- Problems in multiple pregnancy not mentioned.

- Patients may present with inaccurate ideas.
Currently available conditions which can be tested for:

- Klinefelter’s syndrome
- Turner’s syndrome
- Triple X syndrome
- Microdeletions such as 15q
- Di George
- Prader Willi
- Crit du chat
- Single gene disorders e.g. cystic fibrosis
Currently available

- Paternally inherited autosomal dominant conditions or *de novo* mutations, e.g. Huntington’s disease, achondroplasia
- Excluding paternal mutation in autosomal recessive conditions where parents carry different mutations, e.g. B-thalassemia, cystic fibrosis.
- Sex identification for X-linked conditions, e.g. haemophilia
- Patient may know carrier status
  - Family history has resulted in testing
  - Previous affected child
  - Pre-conception testing

- Carrier status may be newly diagnosed in pregnancy
  - Ultrasound markers found in pregnancy

- Routine testing of pregnant women
How is the ethics different for NIPT and prenatal diagnosis generally?

There are many similarities in the ethical issues.

However, the practical and potentially moral advantages of NIPT alter the choices presented to women, families and policy makers. As a result there is a change to the moral nature of prenatal diagnosis.

There is a shift in the balance of ethical principles brought about by the implementation of NIPT.
Checking for thousands of traits with one blood test early in pregnancy could move prenatal genetic testing from uncommon to routine. That possibility challenges all societies to decide for which ends and by what means they want such tests to be used, raising hard questions about, among other things, abortion, disability rights, eugenics and informed consent.
ETHICAL ISSUES

- What ethical questions does it raise for society?
- The individual patient
- Issues of justice and equitable distribution of healthcare
Abortion opponents will want little or no use of tests that will increase the number of pregnancies terminated.

Some people will be concerned about technologies that prevent the birth of people with particular disabilities, both for the message that might send about the worth of those who are disabled and for its practical effects on research, treatment and support for those with disabilities.
A decision to abort based on the fact that the child is going to have specific individual characteristics such as mental retardation, says that those characteristics take precedence over living itself, that they are so important and so negative, that they overpower any positive qualities that there may be in being alive.

I know that amniocentesis can’t tell a parent what kind of child they will have. It can only tell them what disability might exist in that child. Amniocentesis could never have told my mother that I would have artistic talent, an outgoing personality and a sharp wit.

We’ve come to realise that the stereotyped notions of the ‘tragedy’ and ‘suffering’ of the disabled result largely from isolation and exclusion of disabled people from mainstream society.

The mere offering of these tests sets a minimum standard of admission into the living world.
Preimplantation genetic diagnosis and the 'new' eugenics
David S King, Editor, GenEthics News

Professional Issues
Disability Rights, Prenatal Diagnosis and Eugenics: A Cross-Cultural View
Aviad E. Raz
This paper considers the disability rights critique of genetic testing in the context of different communities and the issue of nondirectiveness.

Eugenics Is Alive and Well: A Survey of Genetic Professionals around the World
Dorothy C. Wertz
Division of Social Science, Ethics and Law Shriver Center, Waltham, Massachusetts
Science in Context 1998
Some will oppose parental choices about the characteristics of their babies. Others will worry that parental choice will be influenced, or trumped, by the decisions of governments, health-care systems or other institutions.

Fears of eugenics will increase as such testing moves from fatal diseases to less serious medical conditions and then on to non-medical traits such as skin, hair and eye colour, perhaps, eventually, traits such as some cognitive or physical abilities.

Still other kinds of uses will pose problems. Sometimes, for instance, parents with particular conditions, such as genetic forms of deafness, may want to ensure that their children have the same condition.
Precedent for concerns

Skewing of gender distribution in India following ultrasound sex determination and sex selection.

Pre-implantation genetic diagnosis and trait selection and ‘saviour siblings’.
Ethical issues in the individual

- Potential to undermine informed consent – just another blood test.
- Risk of normalising test as routine – impact on informed consent
- Increased societal pressure to test and terminate
- Misuse of NIPT for minor conditions
- Autonomy – allows women to exercise reproductive autonomy by removing risk of miscarriage, but also threatens autonomy is the ease of the test results in pressure to take it.
- Use of NIPT for information only – justice and equitable distribution of funds. Private access vs access to all.
- Privacy of partner’s rights
Autonomy and informed consent
Because NIPT is safe and easy, danger that it may be presented as a routine blood test without proper explanation.

Also the risk of direct – consumer marketing.

Because the miscarriage risk is no longer there, women may feel they have no reason to say no.

They may have inaccurate ideas, e.g. NIPT is as accurate as amniocentesis/ CVS
Even with proper explanation, women may feel pressurised into having the test. We should not underestimate the subtle power of the offer of a medical procedure by a health care worker in an institutional setting funded by a universal health care program. In these circumstances, the offer may imply a recommendation to accept prenatal screening.
These issues can be addressed by adequate pre-test counselling.

However, if the test is offered to all pregnant women, the resources required for adequate counselling would be enormous.

In addition if NIPT for single gene disorders was offered as a routine to all women, they would need counselling about what these conditions meant.
Barriers to counselling

Time constraints
Inadequate physician knowledge
Insufficient effort to include women in the decision making

Informed decision making is the difference between choice for genetic testing and eugenics
Unlike forced sterilisation and ‘euthanasia’ women are offered a choice about their pregnancy.

Women will make a choice based on limiting suffering in the child and the family.
The process of prenatal screening requires pregnant women to make a decision that is qualitatively different from most other decisions, because of the need to understand and integrate complex and value sensitive concepts where there is no ‘right’ decision.

When deciding whether or not to participate in prenatal screening a woman must consider that further decisions may be necessary about diagnostic testing and termination of pregnancy. These concepts are considered in conjunction with her personal values and circumstances.
A narrow view of autonomy may be problematic. It assumes patients to be self-sufficient, articulate, independent, accustomed to making decisions, possessed of the resources to allow a range of choices. It assumes that physicians have the time, knowledge and communications skills to provide patients with complex information, evaluate the patient's understanding of the information and encourage the patient to make a decision based on her values and preferences without regard for health care costs and legal liability.
Influence of political and social structures

Options available and context are constructed by others

Decisions made by policy makers, researcher and clinicians will affect what information is created, deemed relevant and made available to women.

Influence of personal and public relations

Policy decision to allocate resources to PND may mean less pressure to allocate resources to social and medical programs to help people with the tested for conditions

Guiding clinicians to engage with the woman’s particular family and social situation to facilitate her making an informed choice

Relational autonomy
May not be the best way to achieve autonomous decisions.

May not be possible
- Barrier of persuasive authority
- Counsellor may not identify directive elements
- Terminology such as ‘abnormalities’ may be directive cues
- Verbal and non-verbal cues
- Deciding what information to present and what not to.
- Clinicians’ perspectives and patients’ perspectives may be different and thus neutrality difficult
72% of genetic counsellors acknowledge that they are directive when patients cannot comprehend information because of low education level, cultural or language differences, woman having trouble making a decision.


No correlation between level of knowledge about prenatal diagnosis and patient reporting about whether or not the information was sufficient to make an informed decision.

Dahl et al Ultrasound Obstet Gynaecol 2011
<table>
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<tr>
<th>Information sharing</th>
<th>Non directive counselling</th>
<th>Shared decision making</th>
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<tbody>
<tr>
<td>Clinician imparts objective, value-free information</td>
<td>Clinician and woman share clinical information, personal values (woman) and professional values (clinician).</td>
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| Deliberation | Woman only; clinician cannot express opinion to avoid being directive | Clinician counsels actively in a way that supports the woman to fully understand the information and its implications |

| Decision making | Woman only | Woman only |
JUSTICE
Patient may pay for private NIPT and then be referred to state for further counselling, termination of pregnancy, etc.

This facilitates preferential access to publically funded services which are not available without NIPT.

Women who cannot pay are not excluded only from the test but also from earlier access to genetic counselling and termination.
Rapidly advancing technology

Genome sequencing may result in > 3000 conditions potentially diagnosed by NIPT

Advantages are early testing and no risk of miscarriage
Scenario: Both partners carriers of cystic fibrosis and have one affected child.

Want early diagnosis but would not terminate.

Allows reassurance if negative and time to prepare if positive.

Question regarding use of state resources if management is not changed.
In the future it may be possible for a panel of tests to be offered to parents who are not carriers, i.e. Couples may routinely want reassurance that their child does not have any of the common genetic conditions but may not necessarily terminate.

Potential to have large numbers wanting this as no risk.

How to fund tests that have no immediate clinical benefit.
NIPT and clinical decision making

- For cystic fibrosis, if couple do not terminate, no clinical benefit in knowing beforehand.
- For haemophilia, would be important for clinical management in labour. At this stage can only use NIPT for sex determination in this condition.
- But can do this by doing ultrasound later.
- UK Genetic testing network has not approved NIPT for fetal sex determination in pregnancies at risk for haemophilia.
Psychological risk vs clinical risk

- There are psychological advantages in testing early.
- How are psychological advantages measured against clinical utility to decide whether costs are justified.
- Also the decision to terminate is a complex one and women may not fully be able to decide until they actually have the information.
Are non-clinical outcomes regarded as benefits when measuring cost effectiveness?

Is it acceptable to offer NIPT only to those who say they will terminate? Should it be a tool for deciding on TOP rather than giving information about the pregnancy?

Are there ever circumstances when NIPT can be offered for information when there is no clinical benefit?
Society and NIPT

- Tensions between individuals and society.
- Decreasing the number of people in society with a condition may result in increased stigmatisation.
- Spending increased amounts of money on NIPT means that there may be less money to care for children born with disabilities. Subtle pressure to TOP.
Conclusions

- Technology often outstrips ethics.
- Careful thought out policy guidelines important.
- Consideration of issues of informed consent.
- Equitable distribution of resources.
- Wider societal implications.